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Copper-Catalyzed Asymmetric Conjugate Addition of Grignard Reagents to Trisubstituted Enones. Construction of All-Carbon Quaternary Chiral Centers

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The creation of enantioenriched all-carbon quaternary centers is still a synthetic challenge.[1] Solutions to this problem through the asymmetric conjugate addition[2] have been recently disclosed. We have found that the enhanced Lewis acidity of R_3Al allows the copper-catalyzed conjugate addition to proceed on simple trisubstituted cyclic enones.[3] On the other hand, more reactive substrates, such as nitro-alkenes,[4] or doubly activated enones[5,6] are able to react with R_2Zn. However, there is also another way to tackle the problem: this is to use a more reactive primary organometallic reagent.

It has been long known that lithium dialkyl cuprates, or copper-catalyzed Grignard reagents, are able to undergo conjugate addition to trisubstituted Michael acceptors, thus creating an all-carbon quaternary center.[7] Therefore, we focused our attention on the use of Grignard reagents. It was recently reported that ferrocene-based ligands were appropriate for the enantioselective conjugate addition of Grignards onto several classes of Michael acceptors; however, none of them was trisubstituted.[8] Our attempts to use such ligands with trisubstituted enones were disappointing, the ee's were low and the regioselectivity (1,2 versus 1,4 addition) was poor. On the other hand, all the attempts to use known phosphoramidite ligands gave poor ee's, despite an excellent 1,4 regiocontrol. Our efforts were then focused on finding the right chiral ligands to copper that could induce high levels of enantioselectivity.

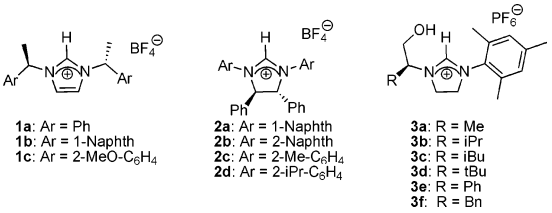
Among the recently described ligands for the copper-catalyzed conjugate addition, the class of diaminocarbenes (or NHCs for *N*-heterocyclic carbenes)[9] has emerged as a viable alternative to phosphorus-based ligands. They do afford an acceleration of the reaction rate,[10] and they also afford high levels of enantioselectivity.[11] The combination of Grignard reagents and NHCs as ligands is unprecedented in the conjugate addition, although an example has been disclosed in the copper-catalyzed allylic substitution.[12]

To begin this study, we performed preliminary tests by reacting different organometallic compounds with 3-methylcyclohex-2-enone **4** (Table 1). The copper-NHC catalyst was prepared in situ by deprotonating the corresponding imidazolidinium salt (ImH^+) with butyllithium in the presence of copper(II) triflate. Three families of chiral ImH^+ were considered (Scheme 1).

From Hermann's-type ligands **1a**−**c**,[9c] we already knew that **1b** was very efficient in the conjugate addition of Et_2Zn to cyclohexenone (89% ee).[11c] However, with **4**, no reaction took place with Et_2Zn.

With Et_3Al and EtMgBr, the conversions were good and a small enantioselectivity was observed (entries 2 and 6). These results were not discouraging, because it is well-accepted that these standard chiral-NHCs often feature low chiral inductions, mainly because of the rapid internal rotation of the chiral substituents around the C−N axis. Thus, considering the possible strategies to lock the N-substituents in fixed conformations, we focused on the C_2-symmetric imidazolidinium **2a**−**d**, bearing chirality on the heterocycle. Their interest lies in the ability of the chiral centers to transfer the chiral information directly in α-position of nitrogens through steric interactions with the a priori achiral N-substituents (Scheme 2).[11d,13]

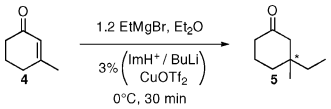
Table 1. Comparison of Organometallics



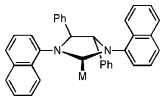
entry	ImH^+	"EtM"	time (h)	conv.[a] (%)	ee[b] (%)
1	**1b**	Et_2Zn	16	1	
2	**1b**	Et_3Al	16	85	9 (−)S
3	**2a**	Et_3Al	16	94	54 (−)S
4	**3b**	Et_3Al	16	94	0
6	**1b**	EtMgBr	0.5	86	17 (+)R
7	**2a**	EtMgBr	0.5	92	68 (−)S
8	**3b**	EtMgBr	0.5	96	61 (+)R

[a] After 16h; determined by GC-MS. [b] Determined by chiral GC Lipodex E.

Scheme 1. Conjugate Addition of Et Grignard and Chiral Ligands



Scheme 2. Transfer of the Chiral Information to the Reacting Center



Interestingly, in this series, the Cu−**2a** complex afforded a promising 54% ee with Et_3Al and 68% ee with EtMgBr (entries 3 and 7). Yet, another strategy is to use bidentate ligands such as the alkoxy-NHCs **3a**−**f** that have demonstrated their efficiency on cyclohexenone and Et_2Zn.[11e−g] The Cu−**3b** complex afforded 61% ee with EtMgBr but no ee with $EtAl_3$ (entries 4 and 8).

We then optimized the experimental conditions for the conjugate addition of EtMgBr to 3-methylcyclohexenone in the presence of a Cu−**2a** complex. The results are summarized in Table 2 of the Supporting Information. The choice of the solvent appeared to be critical. Indeed the best ee (68%; entry 1) is obtained in pure Et_2O, whereas no ee was observed in THF (entry 2). The best temperature for this reaction is 0 °C (entries 1, 6, and 7). $Cu(OTf)_2$ or $Cu(CN)_4$-PF_6 appeared to be appropriate copper sources (entries 1 and 8−11).

Having in hand these operating conditions, we tried to optimize the structure of the chiral ligands. (Table 3 of the Supporting

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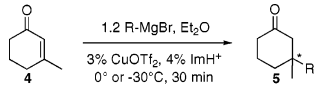
Table 2. Additions of Grignards to **4**



entry	ImH$^+$	R	*T* (°C)	product	conv.[a] (%)	ee[b] (%)
1	**2a**	ethyl	0	ent-**5a**	96(90)	73(S)
2	**3d**	ethyl	0	**5a**	99(81)	80(R)
3	**3d**	butyl	0	**5b**	100	77(R)
4	**3d**	butenyl	−30	**5c**	91(80)	90(S)
5	**3d**	*i*-butyl	−30	**5d**	100(72)	96(S)
6	**3d**	*i*-propyl	−18	**5e**	100(77)	77(R)
7	**3d**	*c*-pentyl	−30	**5f**	100(80)	85(R)
8	**3d**	*c*-hexyl	−30	**5g**	100(79)	74(R)
9	**3d**	*t*-butyl	−30	**5h**	0	
10	**3d**	Ph	−30	**5i**	72(61)	66(R)

[a] Conversion determined by GC-MS. Isolated yields are in parentheses. [b] Determined by chiral GC (Lipodex E).

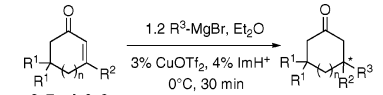
Information). Concerning Hermann's-type ImH$^+$ **1a**−**c**, better results were obtained with the smaller 1-phenyl ethyl substituents (ee up to 55%, entries 1 and 3), rather than 2-ethylnaphthyl (17% ee, entry 2). The case of the imidazolidiniums **2a**−**d** is more tricky; the enantioselectivity decreased following the order 1-naphthyl (68%) > *o*-MeC_6H_4 (63%) ≫ 2-naphthyl (17%) > *o*-*i*-PrC_6H_4 (10%; entries 4−7). With bidentates ImH$^+$ **3a**−**f** (entries 8−13), the enantioselectivity logically increased with the size of the substituent on the chiral center. Slightly better conversions were obtained by adding the substrate on the Grignard reagent slowly. Finally, when adding first the substrate and then the Grignard, the ee drops down, and only 2% ee was obtained (entry 14) with ImH$^+$ **2a**. This may indicate that the active asymmetric species, in the present reaction, is an ate-complex (or higher-order cuprate) such as the type [(NHC)CuEt_2]. This is in contrast with the copper-catalyzed asymmetric allylic substitution, where the Grignard reagent is added very slowly to the substrate to avoid the formation of cuprate species.[14] A last practical modification was made: instead of deprotonating ImH$^+$ with BuLi, we just did it with the Grignard reagent used for the conjugate addition (entry 18). Although the observed ee is slightly lower, this procedure is more convenient and more reproducible.

Next, we explored the scope and limitation of this new methodology. First, a screening of the various Grignard reagents was made with 3-methylcyclohex-2-enone **4** (Table 2). Primary Grignards gave high ee's, up to 96% with *i*-Bu (entry 5). Secondary Grignards behaved as well, particularly when the reaction temperature was lowered to −30 °C. However, *t*-BuMgBr did not react at all, even at a higher temperature. Finally, PhMgBr gave 66% ee of an adduct that cannot be obtained by the Rh-catalyzed conjugate addition of aryl boronic acids.[2c]

Complementary, the addition of EtMgBr was done on various trisubstituted cyclohexenones (Table 3). In all cases, the reaction afforded the desired product in good to moderate ee's. It should be pointed out that even poorly reactive enones, such as isophorone or phenyl cyclohexenone, gave good yields and ee's.

Turning to five- (**10**) and seven-membered rings (**11**), we only tested the addition of EtMgBr, with **3d** as chiral ligand. Although the ee is moderate, this promising result should be improved with better ligands. In conclusion, we have found an efficient way to create, enantioselectively, all-carbon quaternary centers, by the unprecedented asymmetric conjugate addition of Grignard reagents associated with a copper catalyst and a chiral diaminocarbene ligand. There is no need to use specially activated trisubstituted enones, and the scope of the reaction seems wider because many Grignard reagents are easily or commercially available. We strongly believe that new chiral diaminocarbenes, from these laboratories or elsewhere, will improve these first generation ligands.

Table 3. Variation of the Enone



entry	ImH$^+$	enone	*n*	R^1	R^2	R^3	prod.	conv.[a] (%)	ee[b] (%)
1	**2a**	**6**	1	Me,Me	methyl	Et	ent-**10**	93(57)	71(S)
2	**3d**	**6**	1	Me,Me	methyl	Et	**10**	100(85)	82(R)
3	**3d**	**7a**	1	H,H	ethyl	Me	**11a**	98(67)	68(S)
4	**3d**	**7b**	1	H,H	*i*-butyl	Et	**11b**	98(69)	81(S)
5	**3d**	**7c**	1	H,H	phenyl	Et	**11c**	98(87)	72(S)
6	**3d**	**7d**	1	H,H	butenyl	Et	**11d**	99(84)	69(R)
7	**3d**	**8**	0	H,H	methyl	Et	**12**	98(90)	46(R)
8	**3d**	**9**	2	H,H	methyl	Et	**13**	99	82(R)

[a] Conversion determined by GC-MS. Isolated yields in parentheses. [b] Determined by chiral GC (Lipodex E).

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Supporting Information Available: Tables 2 and 3, full experimental data, all chromatograms, and NMR spectra of all new conjugate adducts. This material is available free of charge via the Internet at http://pubs.acs.org.

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